PHILIPS

RESPIRONICS

BiPAP A40 EFL

Hypercapnic COPD with EFL

Prevalence and impact of expiratory flow limitation (EFL) in COPD with a **therapy focus on Hypercapnic COPD**

Authors: Dr. Eui-Sik Suh, MBBS, MChem(Oxon), PhD, FRCP, Consultant Physician in Respiratory and Ventilation Medicine, Lane Fox Respiratory Unit, Guy's and St Thomas' NHS Foundation Trust, London, UK

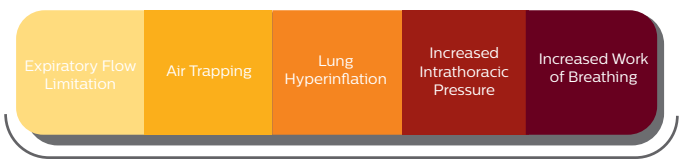
Prevalence of EFL in COPD

Expiratory flow limitation (EFL) during tidal breathing is common in COPD. Among patients with stable COPD in the seated position, prevalence varies between 18%[1] to 73% of patients with mild-to-moderate COPD.[2] Patients who are not flow-limited in the seated position may become flow-limited in the supine position, most likely due to decreases in functional residual capacity, but also due to age-related reductions in airway closing pressure and the presence of obesity.[2]

EFL becomes more prevalent during COPD exacerbations, affecting 31%[3] - 95%[4] of patients requiring hospital admission. Almost all (96%) patients intubated for exacerbation of COPD demonstrate EFL during invasive mechanical ventilation;[5] however, by the time of discharge from the intensive care unit after extubation, EFL is present in just 40% of patients.

There is a clear association between the prevalence of EFL and spirometric severity as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria.[1,2] Patients with less severe disease may be flow-limited only in the supine position, while those with more severe disease are more likely to demonstrate EFL both in the seated and supine positions.

Physiology and consequences of EFL in COPD patients



How does EFL influence outcomes?

Since EFL is the key pathological process that drives dynamic hyperinflation (DH) in patients with COPD, it is unsurprising that there exists a relationship between the presence of EFL and dyspnea (breathlessness). The degree of flow limitation predicts the degree of breathlessness, according to the modified Medical Research Council Dyspnea Scale (mMRC).[1,6] Dyspnea is secondary to DH and is the major cause of exercise limitation in patients with COPD.[7] There is clear evidence that patients with EFL have diminished exercise capacity as determined by the 6-minute walk test (6MWT), compared with non-flow-limited patients.[1] Furthermore, flow-limited patients demonstrate a more rapid decline in exercise capacity over three years.

Exacerbations are key events in the natural history of COPD, as they are associated with increased mortality,[8] impaired quality of life,[9] increased symptom burden and reduced physical activity.[10] The presence of EFL is associated with an increased likelihood, not only of exacerbations, but also of hospital admissions. Perhaps as a result of the increased propensity to exacerbations, flow-limited patients have a higher five-year mortality and shorter time to death, although this effect is driven by patients with mild-to-moderate COPD by spirometric criteria.[1]

The presence of EFL may play a key role in extubation failure in patients with COPD. Vargas et al. studied 35 patients who had been weaned from invasive mechanical ventilation and extubated. The presence of EFL in the hour following extubation was predictive of the post-extubation respiratory failure.[11]

How is EFL detected?

Several methods have been developed to detect EFL, although none have been incorporated into routine clinical practice.

The Fry and Mead-Whittenberger methods are both limited by their invasive nature, requiring the insertion of an esophageal pressure balloon[12, 13] that requires intensive analysis.

In brief, the Fry method involves plotting expiratory flow against esophageal pressure (Pes) during expiratory vital capacity efforts of variable intensity at a given lung volume.[12] EFL is present if no increase in flow occurs despite increasing expiratory effort. The Fry method cannot be used to detect EFL in tidal breathing and requires considerable patient cooperation.

The Mead-Whittenberger method involves plotting a trace of changes in Pes against flow during tidal breathing.[13] Once again, if flow fails to increase despite an increase in expiratory pressure, then EFL is said to be present for that breath. Although this method is considered to be the gold standard for the analysis or detection of EFL in tidal breathing, manual analysis of pressure-flow data is laborious, requires highly specialised analysis and cannot produce results in real time.

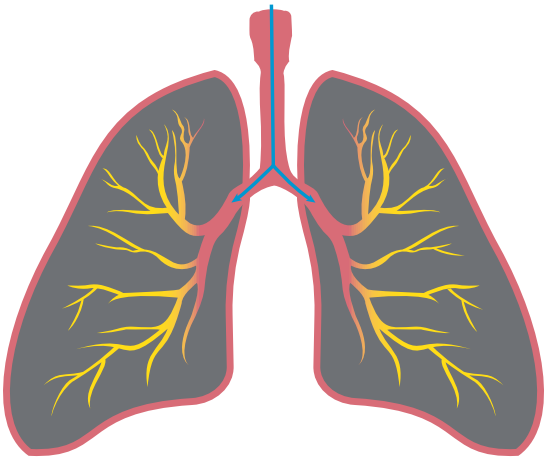
Noninvasive techniques for detecting EFL include the negative expiratory pressure (NEP) and positive abdominal pressure methods. NEP involves the application of a short burst of negative pressure (usually -5 cm H_2O for 30 - 60ms) to the mouth during tidal breathing while monitoring expiratory flow. EFL is present if there is no increase in expiratory flow during the application of negative pressure. Although this technique is well-tolerated, it has limitations in those who have intermittent upper airway obstruction, such as obese patients with obstructive sleep apnea, as the absence of a rise in expiratory flow measured at the mouth under negative pressure may indicate a closure of the upper airways (extra-thoracic flow limitation) rather than of the small airways of the lung (intrathoracic flow limitation). For this reason, some studies have advocated the application of positive abdominal pressure during expiration to detect EFL, although this technique is currently not widely used.[14] Both NEP and positive abdominal pressure techniques require intermittent application of a pressure stimulus to detect EFL.

In light of the fluctuating nature of EFL in response to treatment and postural changes, there is potential utility for a technique that can identify flow-limited breaths in real-time during tidal breathing, such as during nocturnal noninvasive ventilation (NIV) or a severe exacerbation. The forced oscillation technique (FOT) has recently been developed for this purpose.

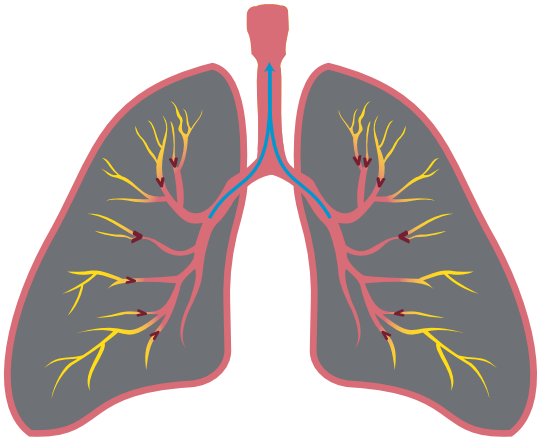
FOT involves the application of sonic oscillations to the mouth to determine the impedance (Zrs) of the respiratory system, which has two components: resistance (Rrs) and reactance (Xrs). The reactance corresponds to the extent to which the phase of the applied oscillations is influenced by the inertial and elastic properties of the respiratory system. One notable property of the reactance is its variation during the respiratory cycle in patients with COPD.

The bronchoconstriction, mucosal edema and mucus plugging that occur in the airways of patients with COPD, coupled with the paucity of tethering of the airways by emphysematous lung parenchyma, increase the tendency for the small airways to close during expiration. In patients with EFL, increasing expiratory driving pressures only serve to exacerbate dynamic closure of the small airways. “Choke points” develop in the small airways during expiration that are not present in inspiration.

Inspiratory Phase in COPD



Expiratory Flow Limitation Choke Points in COPD



When low-frequency forced oscillations are applied to the airway opening, these “choke points” prevent the propagation of the oscillations to the lung periphery during expiration; as a result, the reactance detected using FOT will reflect the elastic properties of the airways proximal to the “choke points”, and magnitude of Xrs will be greater.

By contrast, during inspiration, the airways open and the applied oscillations will readily propagate to the lung periphery. Xrs will consequently reflect the elastic properties of the lung parenchyma, which in COPD are more compliant than the airways, and the magnitude of Xrs will be smaller than during expiration. The within-breath difference in Xrs (termed ΔXrs) should therefore represent the relative extent to which small airway closure occurs in expiration (Figure 1).

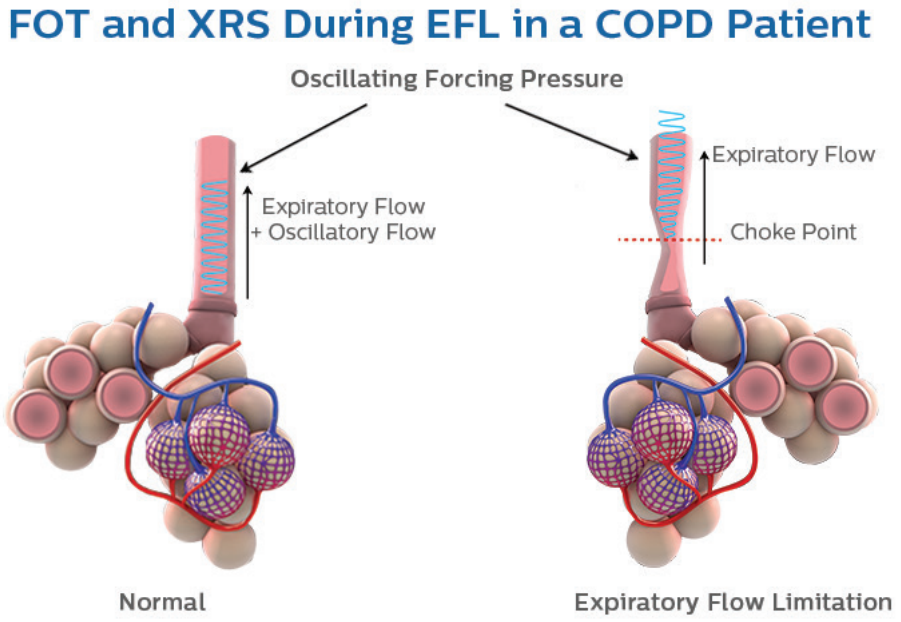


Figure 1. *During inspiration, the applied sound waves or FOT will propagate beyond the small airways, and the reactance (Xrs) will represent the inertial and elastic properties of the lung periphery. During expiration, in the flow-limited patient, choke points in the small airways will impede the propagation of sound waves to the lung periphery, and Xrs will therefore reflect the properties of the lung proximal to the choke points. A difference in Xrs of 2.8 cmH_2O.s.L between inspiration and expiration is indicative of EFL (reference 15).*

Dellaca et al. demonstrated that flow-limited breaths, as identified by the Mead-Whittenberger method, would be detectable using FOT by applying a threshold value of ΔXrs of 2.8 cmH_2O.s.L-1.[15] A further validation study showed that there was good agreement between FOT and the negative expiratory pressure (NEP) technique in identifying patients with EFL.[16] Additionally, when increasing levels of nasal continuous positive airway pressure (CPAP) were applied to flow-limited COPD patients, ΔXrs was observed to decrease below 2.8 cmH_2O.s.L-1 as EFL was abolished.[17] A body of evidence is now emerging around the use of ΔXrs as an indicator of the presence of EFL in patients with respiratory disease. A recent study showed that EFL was present at admission in 95% of patients hospitalised with acute exacerbation of COPD, and that this proportion had fallen to 67% by the time of follow-up, six weeks after discharge.[4]

Importance of evaluating EFL in hypercapnic COPD patients

EFL is an important contributor to hypercapnia in patients with COPD. Progressive DH in COPD patients experiencing an acute exacerbation can lead to a limitation in tidal volume expansion as end-expiratory lung volume rises and the elastic load on the respiratory muscle pump increases. Attempts to increase minute ventilation by increasing respiratory rate only leads to further hyperinflation. Under these conditions, if EFL cannot be alleviated, physiological dead space increases while tidal volume remains constrained, despite escalating central respiratory drive and hypercapnia ensues.

Acute decompensated hypercapnic respiratory failure is a life-threatening emergency, for which the well-established treatment is NIV. While it is critically important to provide adequate inspiratory pressure support to ensure sufficient tidal volumes to eliminate alveolar CO_2, it is also vital to address the EFL that may have caused the hypercapnia in the first place. This may be achieved through judicious

use of end-expiratory positive pressure (EPAP), which acts as a pneumatic splint to maintain airway patency during expiration and may thus abolish EFL. However, an excessive level of EPAP, beyond that which abolishes EFL, may lead to further hyperinflation and thus increase work of breathing. The determination of the optimal level of EPAP in patients receiving NIV has hitherto been a matter of clinical judgement but, recently, FOT has been used in real time, during tidal breathing, to auto-titrate EPAP to a level that abolishes EFL, but does not cause lung hyperinflation. Preliminary data indicate that FOT-based auto-titration of EPAP reduces the work of breathing, intrinsic positive end expiratory pressure (PEEPi) and neural respiratory drive.[18] Furthermore, it may lead to a reduction in nocturnal transcutaneous carbon dioxide levels compared with conventional, fixed-level NIV.[19] FOT-based auto-titration also allows dynamic adjustments to EPAP in response to treatment and changes in posture,[20] according to breath-by-breath detection of EFL.

Patient-ventilator asynchrony is an important contributor to NIV failure in acute hypercapnic respiratory failure. The inspiratory threshold load that arises from EFL can cause delayed or ineffective triggering, leading to poor tolerance of NIV. Again, identifying an appropriate level of EPAP is crucial in alleviating this threshold load, and FOT-based auto-titration of EPAP may help to achieve this.

Importance of targeting EFL as a substrate for intervention in patients with COPD — why might this be superior to standard management?

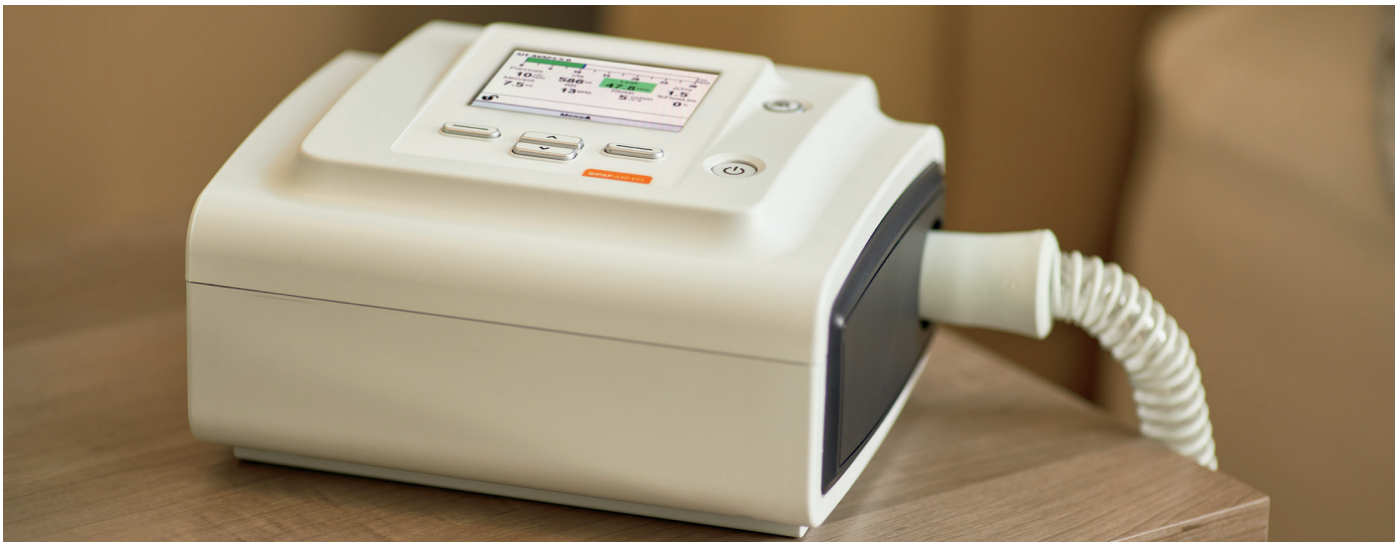
EFL is the key pathological phenomenon driving the derangements in pulmonary mechanics that give rise to the symptoms and impair quality of life in a patient with COPD. Therefore, identifying and addressing EFL should be a priority in the management of COPD. Historically, airflow obstruction, as measured by forced expiratory volume in 1 second (FEV_1), has been the target for pharmacological intervention in COPD.

However, studies are increasingly focusing on measures of DH to determine response to treatment, as they are more closely correlated with symptom burden and as DH is a direct consequence of EFL in a large proportion of COPD patients. Inspiratory capacity (IC) is a good indicator of changes in EELV, and hence of DH, as total lung capacity has been demonstrated to remain unchanged during exacerbations and exercise.[21,22] In fact, a study demonstrated that post-bronchodilator rises in IC were only found in flow-limited patients,[23] further underlining the fundamental link between EFL and DH.

Standard pharmacological treatments do alleviate EFL, of course, with bronchodilator therapy abolishing FOT-determined EFL in 40% of patients in a recent study[24] and leading to improvements in exercise capacity, breathlessness and health-related quality of life. Mucus plugging is a contributor to EFL, particularly during an acute exacerbation, and may be addressed by effective sputum clearance, either through manual or device-driven chest physiotherapy or with mucolytics. While pulmonary rehabilitation has little effect on pulmonary mechanics or airway resistance, there is emerging evidence of its utility in abolishing EFL through its positive effects on breathing pattern.[25]

As discussed previously, in hypercapnic patients with COPD receiving NIV, EFL may be abolished with EPAP that has been judiciously titrated to minimise the work of inspiratory triggering, and hence the work of breathing, while minimising the risk of hyperinflation due to excessive levels of EPAP. This has several potential benefits.

First, it raises the intriguing possibility of using auto-titrated continuous positive airway pressure (CPAP), in the absence of pressure support, to improve breathlessness in patients who have EFL but are not in hypercapnic respiratory failure. Secondly, auto-titrated EPAP offers the opportunity to address, in a dynamic manner, the variations in inspiratory threshold load that arise due to changes in posture, particularly during sleep. Dellaca et al. demonstrated that the optimal EPAP required to abolish EFL in patients with COPD increased from 6 to 10 cmH_2O upon moving from a seated to supine posture.[26] The effects of auto-titrated EPAP on sleep quality among COPD patients receiving domiciliary NIV is as yet undetermined, but it would be reasonable to postulate that sleep efficiency would improve using this approach.



Third, auto-titrated EPAP would be responsive to changes in EFL during an exacerbation. Pharmacological treatment alleviates EFL and inspiratory threshold load, leading to a reduced requirement for EPAP. Fixed-pressure NIV may lead to hyperinflation in patients who are responding to treatment if the EPAP has been set to address the higher PEEPi present at the peak of exacerbation symptoms.

How might optimal management of EFL improve health status?

Abolishing tidal EFL in patients with COPD will give rise to an improvement in dyspnea, given its close association with dynamic hyperinflation. Since dyspnea secondary to DH is known to be a major determinant of exercise limitation, addressing EFL is likely to result in improved exercise capacity and, ultimately, quality of life.

The dyspnea induced by dynamic hyperinflation during an acute exacerbation of COPD is a key cause of hospital admission. Optimal management of EFL at an early stage may therefore reduce the symptoms of an exacerbation and potentially prevent hospitalisation. Since exacerbations and hospital admissions are the outcomes that patients with COPD rate as most important,[27] reducing their frequency and severity will undoubtedly lead to an improvement in health-related quality of life.

Thus far, pharmacotherapy has not been shown to improve survival in COPD patients. By contrast, administering home NIV to patients with chronic hypercapnic respiratory failure has been shown to reduce mortality.[28,29] It would be reasonable to speculate that optimising NIV to address EFL in a dynamic manner through auto-titration of EPAP may offer both enhanced patient tolerance of the intervention and improved physiological outcomes. It is worth noting that these comments require future study and validation to test this hypothesis.

Potential detrimental effects of higher EPAP on comfort

Patients with COPD frequently report nocturnal symptoms and reduction in sleep quality.[30,31] While data on the effects of excessive EPAP on sleep quality are sparse for patients with COPD, the application of high levels of CPAP can worsen breathlessness in patients with obstructive sleep apnea and correlates with sleep compliance.[32] In patients with COPD, a further complication of excessive EPAP is hyperinflation, which can further exacerbate breathlessness. The use of fixed-pressure NIV does not adjust for the changes in PEEPi brought about by changes in posture and breathing pattern during sleep, potentially leading to under-treatment of EFL or lung hyperinflation induced by excessive EPAP. FOT-based auto-titration addresses this challenge by dynamically adjusting EPAP dynamically according to the presence or absence of EFL in real time.

What impact does EFL have on sleep and how might abolition of EFL improve sleep?

While there are no data directly correlating sleep quality with the presence of EFL, a relationship has been reported between the presence of dynamic hyperinflation and reduced sleep efficience.[33,34] Furthermore, Ipratropium Bromide, which counteracts the nocturnal increases in cholinergic tone, has been shown to improve sleep quality and nocturnal gas exchange, presumably through improvements in pulmonary mechanics brought about by lung deflation.[35] Therefore, abolition of EFL may improve sleep quality through improvements in gas exchange, and reduced work of breathing through the reduction of EELV and increased dynamic lung compliance.

References

1. Aarli, B.B., et al., The association of tidal EFL with exercise performance, exacerbations, and death in COPD. *Int J Chron Obstruct Pulmon Dis*, 2017. 12: p. 2179-2188.
2. Koulouris, N.G., et al., A simple method to detect expiratory flow limitation during spontaneous breathing. *Eur Respir J*, 1995. 8(2): p. 306-13.
3. Jetmalani, K., et al., Expiratory flow limitation relates to symptoms during COPD exacerbations requiring hospital admission. *Int J Chron Obstruct Pulmon Dis*, 2015. 10: p. 939-45.
4. Johnson, M.K., et al., Measurement of physiological recovery from exacerbation of chronic obstructive pulmonary disease using within-breath forced oscillometry. *Thorax,* 2007. 62(4): p. 299-306.
5. Alvisi, V., et al., Time course of expiratory flow limitation in COPD patients during acute respiratory failure requiring mechanical ventilation. *Chest*, 2003. 123(5): p. 1625-32.
6. Eltayara, L., et al., Relationship between chronic dyspnea and expiratory flow limitation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*, 1996. 154(6 Pt 1): p. 1726-34.
7. O'Donnell, D.E., Hyperinflation, dyspnea, and exercise intolerance in chronic obstructive pulmonary disease. *Proc Am Thorac Soc*, 2006. 3(2): p. 180-4.
8. Soler-Cataluna, J.J., et al., Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax*, 2005. 60(11): p. 925-31.
9. Suh, E.S., S. Mandal, and N. Hart, Admission prevention in COPD: non-pharmacological management. *BMC Med*, 2013. 11: p. 247.
10. Garcia-Rio, F., et al., Prognostic value of the objective measurement of daily physical activity in COPD patients. *Chest*, 2012.
11. Vargas, F., et al., Respiratory failure in chronic obstructive pulmonary disease after extubation: value of expiratory flow limitation and airway occlusion pressure after 0.1 second (P0.1). *Journal of Critical Care*, 2008. 23(4): p. 577-584.
12. Fry, D.L., et al., The mechanics of pulmonary ventilation in normal subjects and in patients with emphysema. *Am J Med*, 1954. 16(1): p. 80-97.
13. Mead, J. and J.L. Whittenberger, *Physical Properties of Human Lungs Measured During Spontaneous Respiration*. Vol. 5. 1953. 779-796.
14. Ninane, V., et al., Detection of expiratory flow limitation by manual compression of the abdominal wall. *Am J Respir Crit Care Med*, 2001. 163(6): p. 1326-30.
15. Dellaca, R.L., et al., Detection of expiratory flow limitation in COPD using the forced oscillation technique. *Eur Respir J*, 2004. 23(2): p. 232-40.
16. Dellaca, R.L., et al., Expiratory flow limitation detected by forced oscillation and negative expiratory pressure. *Eur Respir J*, 2007. 29(2): p. 363-74.
17. Dellaca, R.L., et al., Noninvasive detection of expiratory flow limitation in COPD patients during nasal CPAP. *Eur Respir J*, 2006. 27(5): p. 983-91.
18. Suh, E.-S., et al., Abolition Of Expiratory Flow Limitation In Severe Chronic Obstructive Pulmonary Disease (COPD) Using Auto-titrating Continuous Positive Airway Pressure Based On The Measurement Of Within-breath Airway Reactance Determined By The Forced Oscillation Technique, in B66. NOVEL AND TRADITIONAL LUNG FUNCTION ASSESSMENT. 2014, *American Thoracic Society*. p. A3555-A3555.
19. Milesi, I., et al., Effects of automatic tailoring of Positive End Expiratory Pressure (PEEP) by Forced Oscillation Technique (FOT) during nocturnal Non-Invasive Ventilation (NIV) in Chronic Obstructive Pulmonary Disease (COPD). *European Respiratory Journal*, 2017. 50(suppl 61).
20. Milesi, I., et al., Effects of posture on tidal Expiratory Flow Limitation (EFLT) and on minimum PEEP(Positive End Expiratory Pressure) able to abolish it in Chronic Obstructive Pulmonary Disease (COPD) patients. *European Respiratory Journal*, 2017. 50(suppl 61).
21. Parker, C.M., et al., Physiological changes during symptom recovery from moderate exacerbations of COPD. *European Respiratory Journal*, 2005. 26(3): p. 420-428.
22. Stevenson, N.J., et al., Lung Mechanics and Dyspnea during Exacerbations of Chronic Obstructive Pulmonary Disease. *Am. J. Respir. Crit. Care Med.*, 2005. 172(12): p. 1510-1516.
23. Tantucci, C., et al., Effect of salbutamol on dynamic hyperinflation in chronic obstructive pulmonary disease patients. *Eur Respir J*, 1998. 12(4): p. 799-804.
24. Dellaca, R.L., et al., Effect of bronchodilation on expiratory flow limitation and resting lung mechanics in COPD. *Eur Respir J*, 2009. 33(6): p. 1329-37.
25. Theodorakopoulou, E.P., et al., Effect of pulmonary rehabilitation on tidal expiratory flow limitation at rest and during exercise in COPD patients. *Respiratory Physiology & Neurobiology*, 2017. 238: p. 47-54.
26. Dellaca, R., et al., Automatic tailoring of positive end-expiratory pressure (PEEP) by forced oscillation technique (FOT) during non-invasive ventilation: Effects of posture and exertion in COPD. *European Respiratory Journal*, 2012. 40(Suppl 56).
27. Zhang, Y., et al., A systematic review of how patients value COPD outcomes. *European Respiratory Journal*, 2018. 52(1).
28. Kohnlein, T., et al., Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. *Lancet Respir Med*, 2014. 2(9): p. 698-705.
29. Murphy, P., et al., S37 Home mechanical ventilation (hmv) and home oxygen therapy (hot) following an acute exacerbation of copd in patients with persistent hypercapnia: results of the per protocol analysis from the hot-hmv uk trial. *Thorax*, 2017. 72(Suppl 3): p. A25-A26.
30. Price, D., et al., Impact of night-time symptoms in COPD: a real-world study in five European countries. *Int J Chron Obstruct Pulmon Dis*, 2013. 8: p. 595-603.
31. Cormick, W., et al., Nocturnal hypoxaemia and quality of sleep in patients with chronic obstructive lung disease. *Thorax*, 1986. 41(11): p. 846-54.
32. Xiao, S., et al., Continuous Positive Airway Pressure and Breathlessness in Obese Patients with Obstructive Sleep Apnea: A Pilot Study. *Sleep*, 2016. 39(6): p. 1201-1210.
33. Kwon, J.S., et al., Hyperinflation is associated with lower sleep efficiency in COPD with co-existent obstructive sleep apnea. *COPD*, 2009. 6(6): p. 441-5.
34. Krachman, S.L., et al., Physiologic correlates of sleep quality in severe emphysema. *Copd*, 2011. 8(3): p. 182-8.
35. Martin, R.J., et al., Effect of ipratropium bromide treatment on oxygen saturation and sleep quality in COPD. *Chest*, 1999. 115(5): p. 1338-45.